DNAJ proteins: more than just "co-chaperones"

Implications for protein aggregation diseases

Vaishali Kakkar

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PROLOGUE

More than 50 years ago, Ferruccio Ritossa, while studying nucleic acid synthesis in ***Drosophila melanogaster*** salivary glands, observed a different "puffing" pattern in the chromosomes of the flies when the incubators were accidently shifted to elevated temperature. Following up this serendipity, he showed that cells can activate a specific transcriptional program when exposed to elevated temperatures, later referred to as "heat shock response". A decade later, Alfred Tissieres discovered the Heat Shock Proteins (HSPs) that were the main products induced by this transcriptional program. The understanding that heat unfolds proteins and they next can form toxic aggregates which could be counteracted by this transient induction of HSPs (via their chaperone actions) provides the basis for the concept of cellular protein homeostasis. All cells are continuously subjected to changes in intra and extra-cellular conditions that impede on protein folding. Further, given the macromolecular crowding within the cells it runs the risk to cause protein aggregation. Protein aggregates hallmark almost all the major neurodegenerative diseases known today, suggesting that an imbalance in the maintenance of protein homeostasis underlies these diseases. This thesis aim at providing an insight into the role of one subset of heat shock protein families, i.e. the class of DNAJ (Hsp40) proteins and the role they play both as cause for and potential therapeutic target in age-related neurodegenerative diseases, with a particular focus on Huntington's Disease.